symptoms of disease: poor grooming, hypoactivity, increased thoracic girth, and increased abdominal girth, hepatosplenomegaly, enlarged thymus, ascites, weakness, squinting, hunching, cachexis, lethargy, and impaired respiration.

94. (New) The method of claim 93, wherein the phenotype comprises at least one of the following: a spleen abnormality, a kidney abnormality a spleen abnormality a liver abnormality, an abnormality of the thymus, an abnormality in the lymph nodes, an abnormality in the lymphocytes, an abnormality in the bone marrow, or an abnormality in the bones.

95. (New) The method of claim 94, wherein the phenotype comprises lymphoma.

96. (New) The transgenic mouse of claim 80, wherein the mouse exhibits lymphoma.

REMARKS UNDER 37 CFR § 1.111

Formal Matters

Claims 1-15, 17-47 and 49 were examined. Claims 11-15, 17-47 and 49 were rejected.

Claims 1-15, 17-47 and 49 have been canceled. New claims 50-96 have been added.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached is captioned **"Version with markings to show changes made."**

Applicants respectfully request reconsideration of the application in view of the amendments and remarks made herein.

Support for the new claims 50-96 can be found throughout the specification, at, for example, page 3, line 1-19, page 6, lines 15-25,page 9, lines 24-29, page 14, lines 14-20. As such, no new matter has been added.

Objection under 37 C.F.R. § 1.75(c).

Claim 2 was objected to under 37 C.F.R. § 1.75(c) because it was asserted that the claim is written in an improper dependent form. The Office Action alleges that Claim 2

fails to further limit the subject matter of a previous claim because "it's unclear how [a screening marker] is different from the 'selection marker'."

Claim 2 is canceled by this amendment. Applicants disagree with the Examiner's assertions and respectfully traverse this rejection. However, as a result of the cancellation of these claims, the Examiner's rejection under 37 C.F.R. § 1.75(c) is no longer relevant.

Further, the Applicants point to the specification of the instant application, which distinguishes a screening marker from a selection marker. A sequence coding for a screening marker, such as, for example, green fluorescent protein (GFP) may be included with a targeting construct so that cells that have undergone homologous recombination may be identified upon exposure to a fluorescent light (Page 10, lines 1-3). In particular, "cells that have undergone homologous recombination will have deleted the GFP gene and will not fluoresce." (Page 13, lines 1-4). As such, a screening marker enables one skilled in the art to visualize cells that have undergone homologous recombination.

In comparison, a sequence coding for a selection marker, such as, for example, a neomycin resistance (*Neo*^{r}) gene may be included with a targeting construct so that cells that have undergone homologous recombination survive and/or grow under certain conditions (Page 12, lines 28-29). For example, cells that express a neomycin resistance gene are resistant to the compound G418, while cells that do not express the neo gene marker are killed by G418. The cells transformed with the targeting construct of the present invention may be subjected to treatment with an appropriate agent that selects against cells not expressing the selectable marker (Pages 7, lines 10-15; page 12, lines 23-31 and page 13, lines 1-25). As such, a selectable marker enables one skilled in the art to distinguish living from non-living cells.

According to the above-reference pages, the Applicants submit that the specification distinguishes a screening marker from a selection marker. Accordingly, the Applicants submit that the term "screening marker" limits the subject matter of Claim 50. Thus, it is argued that Claim 51 meets the requirements of 37 C.F.R. § 1.75(c) by further limiting the claim and as such, Claim 51 is a properly written dependent claim.

Rejection under 35 U.S.C. § 112, 1st paragraph.

Claims 11-15 and 44-47 were rejected under 35 U.S.C. § 112, 1st paragraph for assertedly being non-enabling.

Claims 11-15 and 44-47 are canceled by this amendment. Applicants disagree with the Examiner's assertions and respectfully traverse this rejection. However, as a result of the cancellation of these claims, the Examiner's rejection under 35 U.S.C. § 112, first paragraph is no longer relevant.

Applicants submit that new claims 50-96 are fully described and enabled by the teachings of the application under 35 U.S.C. § 112, first paragraph. As claims 11-15 and 44-47 are no longer relevant as a result of the cancellation of these claims, and new claims 50-96 are fully described and enabled by the application under 35 U.S.C. § 112, first paragraph, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. § 112, first paragraph.

Rejection under 35 U.S.C. § 112, 2nd paragraph.

Claims 1-4, 9-10, 17-39, 41-42 and 46 have been rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

Claims 1-4, 9-10, 17-39, 41-42 and 46 are canceled by this amendment. Applicants disagree with the Examiner's assertions and respectfully traverse the rejection under 35 U.S.C. § 112, second paragraph. However, in view of the cancellation of this claim, the Examiner's rejection is no longer relevant.

The Applicants submit that new claims 50-96 are definite and particularly point out and distinctly claim the subject matter regarded as the invention in accordance with 35 U.S.C. § 112, second paragraph. Applicants respectfully request withdrawal of the rejection under 35 U.S.C. § 112, second paragraph.

Rejection under 35 U.S.C. § 103(a).

Claims 1-8 and 10 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Mansour *et al.* (*Nature* Vol. 336, No. 24, 348-352 (1988)) in view of Medvedev *et al.* (*Genomics* Vol. 46, 93-102 (1997)). Claims 1-8 and 10 have been

canceled. Applicants disagree with the Examiner's assertions and respectfully traverse this rejection. However, as a result of the cancellation of these claims, the Examiner's rejection under 35 U.S.C. § 103(a) is no longer relevant.

The Applicants assert that new claims 50-96 are non-obvious under 35 U.S.C. § 103(a). New claims 50-96 are directed to transgenic animals, cells and methods relating thereto, which have a target gene sequence disrupted by homologous recombination with a sequence homologous to a region of SEQ ID NO: 1. The Applicants assert that the new claims are not obvious in view of the teachings and disclosures of the references cited in the Office Action.

> "To establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation . . . to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) **must teach or suggest all the claim limitations**."
> MPEP § 2143.

The Office Action asserts that, because *Medvedev et al.* "suggest[s] that further studies need to be done . . . [involving] the RORγ gene," (Office Action, page 12) and that knockout technology is described by *Mansour*, that one of ordinary skill in the art would have been motivated to generate a knockout mouse having a disruption in the present RORγ gene, and one would have had a reasonable expectation of success from the combined teachings of the references.

The Office Action asserts that the *Medvedev* reference describes a role of RORγ during fat cell differentiation, implicates RORγ in a variety of malignancies and teaches the cloning of the mouse RORγ gene. As such, the *Medvedev* reference is not concerned with knockout mice. Further, *Medvedev* does not contain any teaching or suggestion of homologous recombination with a region of SEQ ID NO: 1 to generate a RORγ knockout mouse. Thus, *Medvedev* is deficient in making the presently claimed invention obvious because it does not "teach or suggest all the claim limitations." §103.

Mansour *et al.* has been cited for its generalized description of methods for the generation of knockout mice. As such, the reference is not concerned with RORγ knockout mice. In other words, Mansour *et al.* does not contain any teaching or suggestion for the generation of a RORγ knockout mouse, much less the use of SEQ ID NO: 1 for the generation of a RORγ knockout mouse. Thus, Mansour *et al.* fails to make up the fundamental deficiency of *Medvedev et al.*

In view of the cited references, no prima facie case of obviousness has been established. Furthermore, one of ordinary skill in the art would not have been motivated to generate a knockout mouse via homolgous recombination with SEQ ID NO: 1.

Accordingly, presently pending claims 50-96 are not obvious under 35 U.S.C. § 103(a) over Mansour *et al.* in view of *Medvedev et al.*, and this rejection should be withdrawn.

Conclusion.

Applicants submit that all of the pending claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-1271.

Respectfully submitted,
DELTAGEN, INC.

Date: 3/10/03

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

97. (New) A targeting construct comprising:
    (a) a first polynucleotide sequence homologous to a first portion of a RORγ gene;
    (b) a second polynucleotide sequence homologous to a second portion of a RORγ gene; and
    (c) a selectable marker positioned in between the first and the second polynucleotide sequences.

98. (New) The targeting construct of claim 50, wherein the targeting construct further comprises a screening marker.

99. (New) A method of producing a targeting construct, the method comprising:
    (a) providing a first polynucleotide sequence homologous to a first portion of a RORγ gene;
    (b) providing a second polynucleotide sequence homologous to a second portion of a RORγ;
    (c) providing a selectable marker; and
    (d) inserting the first sequence, second sequence, and selectable marker into a vector, to produce the targeting construct.

100. (New) A method of producing a targeting construct, the method comprising:
    (a) providing a polynucleotide comprising a first sequence homologous to a first region of a RORγ gene and a second sequence homologous to a second region of a RORγ gene;
    (b) inserting a positive selection marker in between the first and second sequences to form the targeting construct.

101. (New) An isolated mouse cell comprising a genome comprising a target gene sequence disrupted by homologous recombination of the target gene sequence with a sequence homologous to a region of SEQ ID NO: 1.

102. (New) The cell of claim 54, wherein the cell is an embryonic stem cell.

103. (New) A transgenic mouse comprising a genome comprising a target gene sequence disrupted by homologous recombination of the target gene sequence with a sequence homologous to a region of SEQ ID NO: 1.

104. (New) A cell derived from the transgenic mouse of claim 56.

105. (New) A method of producing a transgenic mouse comprising a genome comprising a target gene sequence disrupted by homologous recombination of the target gene sequence with a sequence homologous to a region of SEQ ID NO: 1, the method comprising:

(h) introducing the targeting construct of claim 50 into a cell;

(i) introducing the cell into a blastocyst;

(j) implanting the resulting blastocyst into a pseudopregnant mouse, wherein said pseudopregnant mouse gives birth to a chimeric mouse; and

(k) breeding the chimeric mouse to produce the transgenic mouse.

106. (New) A method of identifying an agent that modulates the expression of a RORγ gene, the method comprising:

(a) providing the transgenic mouse of claim 56;

(b) administering an agent to the mouse; and

(c) determining whether the expression of RORγ in the mouse is modulated.

107. (New) A method of identifying an agent that modulates the expression of a RORγ gene, the method comprising:

(l) providing the cell of claim 57;

(m)contacting the cell with an agent; and

(n) determining whether expression of the RORγ gene is modulated.

108. (New) A method of identifying an agent that modulates the function of a RORγ gene, the method comprising:

(a) providing the cell of claim 57;

(b) contacting the cell with an agent; and

(c) determining whether the function of the RORγ gene is modulated.

109. (New) The transgenic mouse of claim 56, wherein the transgenic mouse exhibits at least one of the following phenotypes: a spleen abnormality, a kidney abnormality, an abnormality of the thymus, an abnormality in the lymph nodes, an abnormality in the lymphocytes, an abnormality in the bone marrow, or an abnormality in the bones.

110. (New) The transgenic mouse of claim 62, wherein the spleen abnormality is increased weight of the spleen relative to a wild-type mouse.

111. (New) The transgenic mouse of claim 62, wherein the spleen abnormality is increased size of the spleen relative to a wild-type mouse.

112. (New) The transgenic mouse of claim 62, wherein the spleen abnormality is an increased spleen to body weight ratio relative to a wild-type mouse.

113. (New) The transgenic mouse of claim 62, wherein the kidney abnormality is increased weight of the kidney relative to a wild-type mouse.

114. (New) The transgenic mouse of claim 62, wherein the kidney abnormality is increased size of the kidney relative to a wild-type mouse.

115. (New) The transgenic mouse of claim 62, wherein the kidney abnormality is an increased kidney to body weight ratio relative to a wild-type mouse.

116. (New) The transgenic mouse of claim 62, wherein the liver abnormality is increased weight of the liver relative to a wild-type mouse.

117. (New) The transgenic mouse of claim 62, wherein the liver abnormality is increased size of the liver relative to a wild-type mouse.

118. (New) The transgenic mouse of claim 62, wherein liver abnormality is an increased liver to body weight ratio relative to a wild-type mouse.

119. (New) The transgenic mouse of claim 62, wherein the thymus abnormality is increased weight of the thymus relative to a wild-type mouse.

120. (New) The transgenic mouse of claim 62, wherein the thymus abnormality is increased size of the thymus relative to a wild-type mouse.

121. (New) The transgenic mouse of claim 62, wherein the thymus abnormality is an increased thymus-to-body weight ratio relative to a wild-type mouse.

122. (New) The transgenic mouse of claim 62, wherein the abnormality of the thymus is thymic cortical expansion and medullary reduction relative to a wild-type mouse.

123. (New) The transgenic mouse of claim 62, wherein the abnormality of the lymph nodes is depletion of lymph nodes relative to a wild-type mouse.

124. (New) The transgenic mouse of claim 62, wherein the abnormality of the lymph nodes is absence of lymph nodes.

125. (New) The transgenic mouse of claim 62, wherein the abnormality of the lymph nodes is depletion of gut associated lymphoid tissue ratio relative to a wild-type mouse.

126. (New) The transgenic mouse of claim 62, wherein the abnormality lymphocytes comprises lymphoid infiltrates.

127. (New) The transgenic mouse of claim 62, wherein the abnormality lymphocytes is consistent with lymphoma.

128. (New) The transgenic mouse of claim 80, further comprising at least one of the following symptoms of disease: poor grooming, hypoactivity, increased thoracic girth, and increased abdominal girth, hepatosplenomegaly, enlarged thymus, ascites, weakness, squinting, hunching, cachexis, lethargy, and impaired respiration.

129. (New) The transgenic mouse of claim 62, wherein the bone marrow is pale.

130. (New) The transgenic mouse of claim 62, wherein the abnormality of the bones is brittleness.

131. (New) The transgenic mouse of claim 62, wherein the abnormality of the bones is attached white masses.

132. (New) A method of producing the transgenic mouse of claim 62, the method comprising:

(a) introducing a RORγ gene targeting construct into a cell;

(b) introducing the cell into a blastocyst;

(c) implanting the resulting blastocyst into a pseudopregnant mouse, wherein said pseudopregnant mouse gives birth to a chimeric mouse; and

(d) breeding the chimeric mouse to produce the transgenic mouse comprising a disruption in a RORγ gene.

133. (New) A cell derived from the transgenic mouse of claim 62.

134. (New) A cell derived from the transgenic mouse of claim 80.

135. (New) A method of identifying an agent that ameliorates a phenotype associated with a disruption in a RORγ gene, the method comprising:

(a) administering an agent to a transgenic mouse comprising a disruption in a RORγ gene; and

(b) determining whether the agent ameliorates at least one of the following phenotypes: a spleen abnormality, a kidney abnormality a spleen abnormality a liver abnormality, an abnormality of the thymus, an abnormality in the lymph nodes, an abnormality in the lymphocytes, an abnormality in the bone marrow, or an abnormality in the bones.

136. (New) A method of identifying an agent that ameliorates a phenotype associated with a disruption in a RORγ gene, the method comprising:

(a) administering an agent to a transgenic mouse comprising a disruption in a RORγ gene; and

(b) determining whether the agent ameliorates at least one of the following phenotypes: elevated serum alanine aminotransferase, elevated serum alkaline phosphatases, elevated serum aspartate aminotransferase, elevated blood urea nitrogen, and elevated blood phosphorus.

137. (New) A method of identifying an agent that modulates the expression of a RORγ gene, the method comprising:

(d) providing the transgenic mouse of claim 62;

(e) administering an agent to the transgenic mouse; and

(f) determining whether the expression of RORγ gene in the mouse is modulated.

138. (New) A method of identifying an agent that modulates the expression of RORγ gene, the method comprising:

(a) providing the cell of claim 62;

(b) contacting the cell with an agent; and

(c) determining whether expression of the RORγ gene is modulated.

139. (New) A method of identifying an agent that modulates the expression of RORγ gene, the method comprising:

(a) providing the cell of claim 87;

(b) contacting the cell with an agent; and

(c) determining whether expression of the RORγ gene is modulated.

140. (New) A method of identifying an agent that ameliorates a phenotype associated with a disruption in a RORγ gene, the method comprising:

(a) administering an agent to the transgenic mouse of claim 81; and

(b) determining whether the agent modulates RORγ expression in the transgenic mouse, wherein the agent has an effect on at least one of the following symptoms of disease: poor grooming, hypoactivity, increased thoracic girth, and increased abdominal girth, hepatosplenomegaly, enlarged thymus, ascites, weakness, squinting, hunching, cachexis, lethargy, and impaired respiration.

141. (New) The method of claim 93, wherein the phenotype comprises at least one of the following: a spleen abnormality, a kidney abnormality a spleen abnormality a liver abnormality, an abnormality of the thymus, an abnormality in the lymph nodes, an abnormality in the lymphocytes, an abnormality in the bone marrow, or an abnormality in the bones.

142. (New) The method of claim 94, wherein the phenotype comprises lymphoma.

143. (New) The transgenic mouse of claim 80, wherein the mouse exhibits lymphoma.